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(Article begins on next page)

Low birthweight increases the likelihood of severe liver damage in paediatric non-alcoholic fatty liver disease

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List of Abbreviations:

Metabolic syndrome (MetS), non-alcoholic fatty liver disease (NAFLD), small for gestational age (SGA); large for gestational age (LGA), appropriate for gestational age (AGA), NAFLD activity score (NAS), type 2 diabetes (T2DM), non-alcoholic fatty liver (NAFL), non-alcoholic steatohepatitis (NASH), intrauterine growth retardation (IUGR), alanine transaminase (ALT), Body mass index (BMI), standard deviation scores (Z-scores), Waist circumference (WC), aspartate aminotransferase (AST), gamma-glutamyltransferase (GGT), high-density lipoprotein (HDL), low-density lipoprotein (LDL), oral glucose tolerance test (OGTT), Blood glucose (BG), insulin resistance (HOMA-IR), Normal Glucose Tolerance (NGT), impaired fasting glucose (IFG), Impaired Glucose Tolerance (IGT), systolic blood pressure (SBP), diastolic blood pressure (DBP), Portal inflammation (PI)

Abstract

Background and Aims. Intrauterine growth restriction is associated with metabolic syndrome (MetS) and increased risk of non-alcoholic fatty liver disease (NAFLD). Our aim was to investigate the correlation of birthweight with the severity of liver damage in a large cohort of children with NAFLD.

Methods. Two hundred eighty-eight consecutive Caucasian Italian overweight/obese children with biopsy-proven NAFLD were included in the study. Small for gestational age (SGA), large for gestational age (LGA) and appropriate for gestational age (AGA) were defined according to Italian guidelines.

Results. In the whole cohort, 12.2% of patients were SGA, 62.8% were AGA, and 25% were LGA. There was also an inverse association between birthweight and the degrees of steatosis ($\rho = -0.19$, 95% CI $-0.30, -0.08$; $p = 0.001$) portal inflammation ($\rho = -0.20$, $p < 0.001$) and fibrosis ($\rho = -0.177$, $p = 0.003$). SGA children had a higher prevalence of severe steatosis (69%) and severe portal inflammation (14%) compared to the AGA and LGA groups. At multivariate analysis, NAFLD children born SGA had an increased risk of severe steatosis (OR 4.7, $p < 0.001$) and of NAS >5 (OR 3.93, $p = 0.033$), independently of MetS traits. The average birthweight in children with F2/F3 fibrosis was significantly lower than in those with F0/F1 fibrosis. Furthermore, birthweight in children with NAFLD inversely correlated with the levels of pro-inflammatory cytokines, which are increased in SGA children

Conclusions. Low birthweight is an important risk factor for the onset of paediatric NAFLD and for the severity of liver damage early in life beyond and in addition to obesity and insulin resistance.

Keywords: NAFLD, Birthweight, SGA, gestational age, fibrosis, insulin resistance

Introduction

Non-alcoholic fatty liver disease (NAFLD) is the most frequent chronic liver disease worldwide [1], dramatically rising in concert with the epidemics of both adult and childhood obesity and type 2 diabetes (T2DM) [2,3]. NAFLD includes two distinct phenotypes with different histologic features and prognoses: non-alcoholic fatty liver (NAFL) or simple steatosis and non-alcoholic steatohepatitis (NASH); the latter represents the progressive form of NAFLD and is featured by hepatocellular injury, inflammation, and various degrees of fibrosis, up to advanced fibrosis and cirrhosis [4].

Traditionally considered the hepatic manifestation of the metabolic syndrome (MetS), NAFLD is a multifactorial disease with a substantial inter-patient variability in terms of severity and rate of progression [5-7]. In obese children, NAFLD and NASH have a general prevalence of 70 and 30%, respectively [8]. In the paediatric setting, intrauterine environment may play a pivotal role in the onset and progression of NAFLD [5,9]. Perturbations of intrauterine environment during pregnancy (i.e. placental insufficiency) may deeply affect foetus growth causing intrauterine growth retardation (IUGR) [10,11]. The American College of Obstetricians and Gynecologists has defined small for gestational age (SGA) a newborn with an actual birthweight below the 10th weight percentile for his/her age in gestational weeks [12]. During the first years of life, most children born SGA (70%–90%) exhibit the phenomenon of “catch-up growth”, which is associated to an increased risk of metabolic alterations and T2DM later in life [13,14], but whether this is due to environmental or genetic causes is still controversial. According to the “thrifty phenotype” hypothesis, a hostile intrauterine environment may induce the activation of endocrine mechanisms and gene reprogramming leading to reduced insulin secretion and increased insulin resistance [15]. On the contrary, the “foetal insulin hypothesis” suggests that alterations in insulin sensitivity and secretion in newborns with intrauterine growth reduction are genetically determined and independent of the intrauterine environment [16]. In any case, at birth, when nutrient availability is higher, this "greedy" metabolism may cause fast weight gain and

fat accumulation predisposing children with IUGR both to MetS and NAFLD in adulthood and increasing the risk of cardiovascular mortality [5,9,17].

In a previous study performed in a small cohort of children, we have shown the association of paediatric NAFLD with intrauterine growth retardation independent of and in addition to insulin resistance. [18]. However, the impact of birthweight on the histologic features of liver damage remains incompletely characterized. This study is undertaken to further investigate the association between birthweight, NAFLD severity at histology and clinical components of the MetS in a larger cohort of Italian children with biopsy-proven NAFLD.

Patients and Methods

Study population

We studied 288 Caucasian Italian children with NAFLD, consecutively observed in the Liver Unit, “Bambino Gesù” Children’s Hospital, Rome, Italy, from June 2001 to December 2015. Liver biopsy was performed in all of them because of alanine transaminase (ALT) elevation > 6 months and ultrasound evidence of hepatic steatosis, according to the guidelines of the European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPHGAN) [19]. In all of them, chronic liver disease of other aetiology, including viral, alcoholic, autoimmune and genetic (inborn alterations of metabolism, Wilson’s and 1-alpha-antitrypsin-deficiency) had been previously ruled out.

The study was approved by the Institutional Review Board (IRB) of the “Bambino Gesù” Children’s Hospital, Rome, Italy. Informed consent was obtained from each patient and guardian.

All children underwent a complete physical examination at the time of diagnosis of NAFLD. Medical history and anthropometric data at birth were collected from their medical records and hospital charts. Gestational age data expressed in weeks. Small for gestational age (SGA) and large for gestational age (LGA) were defined as birthweight at <2SD (10th percentile) and > 2SD (90th percentile) for gestational age, respectively. Birthweights between the 10th and 90th percentiles were defined as appropriate for gestational age (AGA). Italian specific growth charts [20] were used to define the 3 different categories of birthweight corrected for gestational age and sex [21].

Anthropometric data were collected at the time of liver biopsy. Weight was measured by a conventional scale with a precision of 100 g and height was measured by a Harpenden stadiometer with a precision of 1 mm. Body mass index (BMI) was expressed in kilograms per square meters. BMI standard deviation scores (Z-scores) were calculated, according to population-specific reference data [22]. Waist circumference (WC) was measured with a tape to the nearest 0.5 cm measure, at the narrowest circumference between the lower costal margin and the iliac crest in standing position.

Laboratory tests

Blood sampling was performed at the time of liver biopsy after an overnight fast. Laboratory tests by automated commercial methods included: ALT, aspartate aminotransferase (AST), and gamma-glutamyltransferase (GGT), high-density lipoprotein (HDL)-cholesterol, low-density lipoprotein (LDL)-cholesterol, total cholesterol, triglycerides, and uric acid.

The circulating levels of TNF- α , IL-1 and IL-6 were measured according to the manufacturer's recommendations by commercially available ELISA kits (BioVendor, Heidelberg, Germany).

All patients also underwent an oral glucose tolerance test (OGTT)(1.75 g/kg, maximum 75 g) with glucose and insulin assessments at time 0, 30, 60, 90 and 120 min. Blood glucose (BG) was measured by the glucose oxidase technique (Cobas Integra; Roche, Basel, Switzerland). Insulin was measured by chemiluminescence on ADVIA Centaur analyser. Intra- and inter-assay variability coefficients were 4 and 5.5%, respectively. All insulin determinations were performed in the same laboratory.

The homeostasis model assessment of insulin resistance (HOMA-IR) was calculated according to the formula: [(fasting plasma insulin in mU/l) x (fasting plasma glucose in mmol/l)/22.5]. A cut off of HOMA-IR >2.5 was considered indicative of insulin resistance as previously reported [23,24].

Glucose tolerance was defined according to the American Diabetes Association criteria [25]; (BG) <100 mg/dl (5.5 mmol/l) is considered Normal Glucose Tolerance (NGT), BG> 100 and <125 mg/dl (5.5-6.9 mmol/l), impaired fasting glucose (IFG) and BG \geq 126 mg/dl (7.0 mmol/l) type 2 diabetes T2DM. The OGTT (BG at 120') was used to further categorize all study subjects into normal glucose tolerance (NGT) (BG <140 mg/dl or 7.8 mmol/l). Impaired Glucose Tolerance (IGT) (BG>140 mg/dl or 7.8 mmol/l and <199 mg/dl or 11.1 mmol/l) and T2DM (BG \geq 200 mg/dl or 11.1 mmol/l)

Blood pressure measurement

All patients underwent a 24-h blood pressure measurement (ABPM) (Spacelab 90207, Spacelab Inc, Redmond, WA equipped with an adequate cuff-size). The device recorded measurements every 15

min from 7:00 a.m. to 11:00 p.m. and every 30 min from 11:00 p.m. to 7:00 a.m. Measurements of a pulse pressure of less than 20 mmHg, or a heart rate of less than 40 beats per minute, were considered errors and excluded automatically by the device . At least 75% of successful measurements were needed to be accepted. Wake and sleep periods were established by a daily activities diary kept by each patient. Diagnosis of hypertension was made according to tables of oscillometric mean ABPM values for healthy children adjusted for gender and height [26].

Metabolic syndrome definition

MetS was defined by the presence of 3 or more of the following five criteria: abdominal obesity as WC $\geq 90^{\text{th}}$ percentile for age [27]; plasma triglyceride levels $> 95^{\text{th}}$ percentile for age and sex [28]; HDL cholesterol level $< 5^{\text{th}}$ percentile for age and sex [29]; systolic (SBP) or diastolic blood pressure (DBP) $> 95^{\text{th}}$ percentile for age and sex [30].

Liver histology

Liver biopsy was performed after an overnight fast, using an automatic core biopsy 18 gauge needle (Biopince, Amedic, Sweden) under general anaesthesia and ultrasound guidance. Samples with a length of at least 15 mm and including at least 6 complete portal tracts were considered adequate for the purpose of the study. Biopsies were routinely processed (i.e., formalin-fixed and paraffin-embedded). Sections of liver tissue, 5-mm thick, were stained with hematoxylin–eosin, Van Gieson, periodic acid-Schiff diastase, and Prussian blue stain. Liver biopsy features for each case were graded according to the NAFLD activity scoring (NAS) system proposed by Kleiner et al. [31]. In addition, individual histological features of NAFLD were scored as follows: steatosis (0-3), lobular inflammation (0-3), ballooning (0-2), and portal inflammation (0-2). Portal inflammation (PI) was further categorized as absent (0), mild (1) and moderate (2). Mild PI was defined as a few mononuclear cells, in more than one portal tract. Moderate PI was defined as one portal area showing moderate to marked density of inflammation, and/or the presence of lymphoid aggregates as proposed by Brunt et

al. [32]. Fibrosis was scored as 0 – none; 1 – periportal or perisinusoidal fibrosis; 2 – perisinusoidal and portal/periportal fibrosis; 3 – bridging fibrosis; and 4 – cirrhosis. NASH was defined as the presence of combined hepatic steatosis, inflammation and ballooning, with or without fibrosis, according to the American Association for the Study of Liver Diseases (AASLD) guidelines [33]. A NAS > 5 was used for further comparisons with variables of interest.

Statistical analysis

Data are reported as mean \pm standard deviation for normal continuous variables, median (25th-75th percentiles) for not normally distributed continuous variables and frequencies (%) for categorical variables. Differences between groups were evaluated with the t-test if variables were normally distributed or with the non-parametric Mann-Whitney test if variables were not normally distributed. For categorical variable, differences between groups were assessed with the χ^2 test or with the χ^2 test for trend as appropriate. The association between the birthweight and histological features or inflammatory markers were assessed by the Spearman correlation analysis. Univariate and multivariable logistic regression analysis were performed to evaluate predictors of significant fibrosis ($F \geq 2$) and severe steatosis ($\geq 66\%$). A p value <0.05 was considered statistically significant. All analyses were performed using MedCalc Software bvba, version 12.7.0.0.

Results

Study population

A total of 288 consecutive overweight/obese children (133 males, 155 females), in an age range 6-17, were diagnosed NAFLD at liver biopsy and were included in the present study. All of them were born at term (≥ 37 weeks). In the whole NAFLD population, 35 patients were born SGA (12.2%), 181 were AGA (62.8%) and 72 were LGA (25%). Overall, 37 children (13%) met the diagnostic criteria for MetS. None of them had Type 2 diabetes, but 30% had an Impaired Glucose Tolerance according to OGTT. The prevalence of MetS was 20% in children born SGA, 9% in those born AGA and 18% in LGA. Taking into account each metabolic feature, waist circumference and blood glucose were increased in LGA compared to the other classes (p for trend <0.001 and $=0.029$, respectively), while HDL cholesterol was lower in SGA (p for trend <0.001).

Table 1 shows the clinical, anthropometric and biochemical variables of the study subjects subdivided in NAFL or NASH according to liver histology. NASH was diagnosed in 76% of the patients. The percentage of children with at least one feature of MetS in the whole population was very high (91%), and similar in NAFL and NASH subjects ($p=ns$). However, children with NASH had more raised values of systolic blood pressure, fasting glucose, insulin and HOMA-IR compared to NAFL.

Effect of birthweight on the severity of liver disease in children with NAFLD

When the whole cohort of NAFLD children were subdivided according to histology, the prevalence of SGA in the NASH group was 1.5-fold higher compared to the NAFL, while the prevalence of AGA and LGA were similar in the two groups (**Table 1**).

To examine the impact of birthweight on liver damage in this paediatric cohort, we evaluated the differences in each histological feature according to being born SGA, AGA or LGA (**Table 2**).

NAFLD patient born SGA had a higher prevalence of severe steatosis (>66%) and severe portal inflammation (grading 2) compared to the AGA and LGA groups (p for trend=0.021 and 0.002, respectively), while lobular inflammation and ballooning were unaffected by birthweight.

The distribution of the degrees of steatosis and portal inflammation in NAFLD children according to their weight at birth is shown in **Figure 1**. Strikingly, severe steatosis (>66%) was decreasing from SGA to AGA and LGA (p=0.006); a similar trend was also observed for portal inflammation (p=0.002). The Spearman correlation between the birth size of NAFLD children and their histological parameters confirmed the inverse association between birthweight, degrees of steatosis (rho= -0.19, 95% CI -0.30,-0.08; p=0.001) and of portal inflammation (rho=-0.20, 95% CI -0.31,-0.09; p<0.001).

Significant fibrosis (F2-F3) was more common in the AGA group, which obviously was the largest group of children (**Table 2**). Nevertheless, the Spearman correlation showed that the birthweight was inversely correlated also with the severity of fibrosis (rho= -0.177, 95% CI -0.29, -0.06; p=0.003). In keeping with this, the average birthweight in children with moderate/severe fibrosis (F2/F3) was significantly lower than in those with F0/F1 fibrosis (2938 ± 562 vs 3206 ± 572 g, p<0.001) (**Figure 2**).

Univariate or multivariable regression for the association of birthweight with NAFLD and MetS traits

At univariate analysis, severe steatosis was associated with birthweight, raised liver transaminases, and increased fasting glucose and insulin levels, HOMA-IR and SGA. At multivariate analysis, SGA at birth was the variable most significantly linked to severe (>66%) steatosis. NAFLD children born SGA had an almost 5-fold increased risk of severe steatosis (OR 4.7, 95% CI 1.9-11.4, p<0.001) independently of insulin resistance and components of MetS (**Table 3**). On the contrary, SGA at birth did not result as an independent predictor of portal inflammation or fibrosis both at univariate and at multivariate analysis (**Supplementary Table 1** and **Supplementary Table 2**).

At univariate analysis, a NAS>5 was associated with liver function tests, fasting glucose and insulin levels and HOMA-IR, raised blood pressure and birthweight (**Table 4**). At multivariate analysis, being SGA was the strongest predictor of NAS>5, increasing almost 4-fold its likelihood probably because of its impact on steatosis (**Table 4**).

Inflammatory markers and birthweight in children with NAFLD

In order to provide an explanation for the worse histologic profile of NAFLD children born SGA compared with the AGA and LGA, we assessed in our study population the plasma levels of tumour necrosis factor (TNF)- α , interleukin (IL)-6 and IL-1 β , considered the most relevant markers of systemic inflammation in children with NASH [34].

The Spearman correlation showed that birthweight negatively correlated with the levels of TNF- α (rho= -0.721; 95% CI -0.779,-0.650; p<0.0001) and IL-6 (rho= -0.389; 95% CI -0.497,-0.269; p<0.0001) and IL-1 β (rho= -0.185; 95% CI -0.311,-0.053; p=0.0049).

Discussion

Intrauterine growth retardation (IUGR) is associated with the development of clinical manifestations of the MetS and increased cardiovascular risk in adulthood [10] and is a strong risk factor for NAFLD since childhood [17, 18]. We had previously shown the association of paediatric NAFLD with IUGR; the prevalence of SGA in children with NAFLD resulted about four times higher compared to the average percentage of the hospitalized children [18]. The current study further extends our knowledge on the impact of SGA on each single feature of histological liver damage in paediatric NAFLD. In our large and well-characterized cohort of children with NAFLD, we found that SGA *per se* is an important risk factor for the severity of histologic liver damage, beyond well-established risk factors such as insulin resistance and components of the MetS.

In large epidemiological studies, birthweight is related with adulthood liver fat. In 2,003 Finnish adults, a significant association between adulthood liver fat score (based on five variables: presence of MetS, T2DM, fasting serum insulin, AST and ALT levels, and AST/ALT ratio) and birthweight was observed in women [35]. Recently, in the Cardiovascular Risk in Young Finns Study [36], the risk of adult NAFLD (assessed by ultrasound) after a follow-up of 31 years was associated with low birthweight in addition to well-known variables. The odds ratio for SGA was 1.71 (95% confidence interval 1.07-2.72, $P=0.02$), higher than BMI (OR 1.30), fasting insulin levels (OR 1.25), and the common PNPLA3 I148M (allelic OR 1.63) and low-frequency TM6SF2 E167K (allelic OR 1.57) variants.

However, none of the above-mentioned studies examined liver histology. Besides being a risk factor for NAFLD, our study reveals that SGA is able to increase 5-fold the likelihood of severe steatosis early in childhood, beyond and in addition to other well-known risk factors. Causative mechanisms linking the severity of liver damage in NAFLD with gestational age at birth are still under investigation. Rapid weight catch-up growth, a major risk factor for later development of insulin-

related complications, can be implicated in the presence and severity of NAFLD in both children and adults [37]. However, in the Finnish study [36], low birthweight was associated with adult fatty liver even when adjusted with childhood BMI and insulin levels, suggesting that this association cannot be simply explained by catch-up growth after IUGR. Similarly, in our study, the link between SGA and liver damage was independent and in addition to insulin resistance, reflecting a more profound alteration possibly related the adverse intrauterine environment. Studies in adults and children born SGA indicate that insulin resistance is the earliest component associated with low birthweight, irrespective of confounding factors, including obesity and a family history of T2DM [37-39]. Nutrition in an adverse intrauterine environment during foetal life can be able to trigger a metabolic adaptation by epigenetic regulation of gene expression and thereby permanently sets functional capacity, metabolic competence, and responses to the later environment that favour NAFLD [40]. Furthermore, liver growth itself may be impaired and reduced as part of the adaptive response to a poor foetal substrate supply [40].

Fibrosis is the histological feature where the association with SGA was less apparent, although there was an inverse relationship with weight at birth. Probably this study is underpowered to detect an association between birthweight and fibrosis, due to the low number of children with SGA and to the low prevalence of severe fibrosis in this paediatric cohort: only two patients had severe (F3) fibrosis while the majority (73%) had no or negligible fibrosis (F0/F1). Chronic liver diseases progress slowly and both experimental and clinical data have shown that older age is a major accelerator of fibrogenesis [41]. In NASH, advanced fibrosis and cirrhosis are exceedingly rare in young individuals and age higher than 50 is one of the strongest fibrogenic predictor [42]. In the last years, increased circulating levels of IL-6 and TNF- α were found in cord blood of SGA children compared to AGA [43]. We previously reported that fatty liver in obese children is characterized by increased production of pro-inflammatory cytokines, such as IL-1 β , IL-6, TNF- α , secondary to stimulation of the endotoxin-

induced toll-like receptor 4 signalling and strongly associated with the severity of NASH-related liver damage [34, 44, 45]. In our cohort, we found a negative correlation between TNF- α , IL-6 and IL-1 β circulating levels and birthweight. The significant increase of the level of these cytokines in NAFLD children born SGA may partially explain the pathological connection between liver damage and low birthweight, even if further studies are required to confirm this hypothesis.

In conclusion, low weight at birth is an important risk factor for not only the onset of paediatric and adult NAFLD but also for the severity of liver damage early in life beyond and in addition to obesity, T2DM and insulin resistance.

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V.N. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Table 1. Clinical and biochemical characteristics of the study cohort according to the diagnosis of NASH.

	All subjects (N=288)	NAFL (N=69)	NASH (N=219)	<i>p</i> value
Age, years	13 ± 2.6	12.8 ± 2.7	13.2 ± 2.6	0.124
BMI, kg/m ²	28.8 (26-31.4)	28.2 (25.3-31.8)	28.8 (26-31.3)	0.855
Waist, cm	88 (79-97)	87 (78-95)	88 (79-97)	0.222
Birthweight, g	3220 (2820-3530)	3340 (3000-3600)	3100 (2820-3530)	0.077
Gestational Age, weeks	37.7 ± 2.2	37.6 ± 3.9	38 ± 1.3	0.001
AST, UI/L	27 (24-38)	25 (20-26)	31 (25-42)	<0.001
ALT, UI/L	39 (26-58)	23 (19-35)	40 (32-70)	<0.001
GGT, UI/L	22 (17-26)	14 (11-23)	23 (19-40)	<0.001
Uric Acid, mg/dL	6 (4.7-6.7)	5.6 (4.6-6.4)	6 (5-6.8)	0.046
Total Cholesterol, mg/dL	156 (134-167)	157 (147-170)	156 (130-166)	0.060
HDL-Cholesterol, mg/dL	47 (34-65)	47 (39-58)	47 (32-66)	0.800
Triglycerides, mg/dL	95 (69-156)	100 (80-145)	93 (69-160)	0.910
Glucose, mg/dL	80 (73-88)	77 (70-81)	85 (75-89)	0.001
Glucose 120', mg/dL	109 (102-116)	110 (99-117)	109 (102-116)	0.691
NGT/IGT/DM (%)	80/20/0	70/30/0	84/16/0	0.797
Insulin, □U/L	19.5 (17.7-28.3)	17.7 (12.7-22.6)	21.7 (18-28.8)	<0.001
Insulin 120', □U/L	111 (84-169)	115.4 (94.6-165.4)	110.4 (82-177)	0.949
HOMA-IR	4.09 (3.30-5.78)	3.26 (2.21-4.40)	4.17 (3.59-6.04)	<0.001
SBP, mmHg	114 (106-130)	108 (101-126)	116 (110-130)	0.001
DBP, mmHg	67 (59-78)	66 (56-72)	68 (59-78)	0.082
SGA/AGA/LGA, n	35/181/72	6/46/17	29/135/55	0.575
(%)	(12.2/62.8/25)	(8.7/66.7/24.6)	(13.3/61.6/25.1)	

Data are reported as mean ± standard deviation for normal continuous variables, as median (25th-75th percentiles) for non-normal continuous variables and as number (%) for categorical variables. AGA, appropriate gestational age; ALT, alanine-aminotransferases; AST, aspartate aminotransferases; BMI, body mass index; DBP, diastolic blood pressure; DM, diabetes mellitus; GGT, gamma-glutamyl aminotransferases; HDL-Cholesterol, high density lipoprotein cholesterol; HOMA-IR, homeostasis model of assessment-insulin resistance index; IGT; impaired glucose tolerance; LDL-Cholesterol, low density

lipoprotein cholesterol; LGA, large gestational age; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; NGT, Normal Glucose Tolerance; SBP, systolic blood pressure; SGA, small gestational age.

Figure Legends

Figure 1. Distribution of degrees of steatosis (A) and portal inflammation (B) according to birthweight in children with NAFLD. AGA, appropriate gestational age; Infl, inflammation; LGA, large gestational age; S, steatosis; SGA, small gestational age.

Figure 2. Distribution of birthweight according to the degree of fibrosis in children with NAFLD.